## REMARKS

Claims 1-53 are pending in this application. Claims 2-3, 6, 15, 17-28, 40 and 48 are cancelled. Claims 1, 4, 7-9, 11-14 and 16 are amended.

## Information Disclosure Statement

On April 25, 2006 an Information Disclosure Statement (IDS) was electronically filed. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in this application. Applicants further request that the Examiner initial and return the form PTO/SB/08 in accordance with MPEP §609, which form was also filed on April 25, 2006. Applicants reserve the right to establish patentability of the claimed invention over any of the information provided therewith, and/or to prove that such information may not be prior art, and/or to prove that his information may not be enabling for the teachings purportedly offered. Applicants wish to direct the Examiner's attention to particular items in the above IDS, such as declarations of Marshall, Eutick and Moyer, which were filed in connection with the opposition proceedings in Australia in the corresponding application to the instant application.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

## I. Support for Amendments

The limitation Ready-to-Use finds support throughout the instant disclosure, including p. 3, ll. 8-20, 24-30; p. 6, ll. 8-13, 15-18; p. 13, ll. 5-20, especially ll. 9-11; p. 20, Example 1; p. 21, Example 2 and Table 2; and p. 22, ll. 1-8. In each case, one of skill will recognize that the formulations disclosed are stable and ready-to-use without re-constitution as is required in the prior art.

Further, regarding the limitation "+/- 0.2", this limitation was present in claim 4 as originally filed.

In addition, with respect to claims 14 and 16, the Office should kindly note that the claims are amended to simplify the issues and consolidate the number of claims. In particular, claims 14 and 16 are amended to include the buffered saline at pH 5.6, i.e., 100mM sodium chloride, 10mM succinate buffer at pH 5.6, 0.5 mg/mL serum albumin and botulinum type B at a concentration of 5,000+/- 1000 U/mL. The specification provides explicit support for said amendments (e.g., p. 21, Table 1; now canceled claims 18, 23, 24, 28).

## II. Finality of Office Action mailed December 8, 2005 is improper

Applicants respectfully request the Office withdraw finality, because grounds of rejection newly raised the Final Action are not based on material changes to the claims. The Final Action sets forth art rejections grounded on a new interpretation of a limitation that was properly before the Office prior to the Office Action mailed July 21, 2005. In view of these new grounds of rejection, the Office Action mailed December 8, 2005 is inadmissibly designated as Final.

First, the art rejections are indicated to be necessitated by amendments to the claims. However, the art rejections are in fact based on a limitation that was already present. In particular, the Office submits rejections under 35 U.S.C. §§ 102 and 103 that are entirely grounded on a newly presented interpretation for the limitation "buffered saline", a limitation present in the claims prior to the Action mailed July 21, 2005. *See*, Section III, *infra* (discussing claim interpretations regarding "buffered saline"). More particularly, the Final Action states, "[t]he limitation 'buffered saline' is interpreted as being same as 'buffer' in this rejection." Final Action, p. 10, last ¶. Independent claims 1 and 16 recited the limitation "buffered saline" prior to the office action mailed July 21, 2005. However, nowhere in the Action mailed July 21, 2005 does the Office set forth the preceding interpretation of "buffered saline", which interpretation forms the basis of the §§ 102 and 103 rejections in the Final Action. It is clear that the Office had ample opportunity to assess the claims and submit this interpretation previously thus providing Applicants an opportunity to respond to such an interpretation.

Furthermore, the Office asserts that the newly introduced amendments are allegedly functional limitations that do not define the formulation structurally. (Final Action, p. 10, last ¶; p.

11, ¶ 1; p. 12, ¶ 2). Therefore, because the Office sets forth a new interpretation for "buffered saline" as forming the basis for art rejections, and because additional amendments are deemed functional limitations, it is respectfully asserted the Final Action comprise new grounds of rejection that were not necessitated by amendment. As such, the finality of the Office Action mailed on December 8, 2005 is improper and should be withdrawn.

## III. Claim Interpretation of "Buffered Saline" is improper

In the Final Action, the Office takes the position that the limitation "buffered saline" is indistinct from "saline". Final Action, p. 2. Furthermore, the Office asserts that the term "buffered saline" is not defined either implicitly or explicitly anywhere in the instant disclosure. *Id.* In addition, the Final Action recites, "[w]hile there is a description herein of 'physiological buffer', there is no recitation of a 'physiological' saline or 'isotonic' saline." Final Action, p. 2, ¶ 1. It is unclear how the preceding sentence bears on the interpretation of "buffered saline". The instant claims do not recite the limitations "physiological saline" or "isotonic saline".

In other words, the issue is whether "buffered saline" and "saline" are of a distinct scope and/or meaning. Thus, whether the saline is isotonic or physiological is irrelevant to the interpretation of "buffered saline" as compared to "saline". If however, the Office intended to provide an interpretation of "buffered saline" and regarding whether such a formulation is "pharmaceutically acceptable", then it is respectfully pointed out that "buffered saline" is unambiguously characterized to be "pharmaceutically acceptable" in the instant disclosure, as further discussed herein below. Furthermore, after assessing the full disclosure including specific examples therein, it would remedial for one of ordinary skill in the art to understand the meaning of "buffered saline". For example, in p. 20, ll. 1-20, the specification describes a formulation of 2.7 mg/mL disodium succinate and 5.8 mg/mL sodium chloride (i.e., saline) adjusted to a pH of 5.6, thus presenting an explicit example of a "buffered saline" with both the buffering and saline components identified.

Therefore, as to the Office's interpretation of "buffered saline" and "saline", Applicants respectfully submit that although the terms "buffered saline" and "buffer" perform the same function

of buffering, they nonetheless do not have the same scope or meaning as put forth by the Office. More specifically, "buffered saline" further limits the term "buffer" in the context of a suitable formulation for use in the present invention. In other words, while a "buffered saline" does provide buffering capacity, a "buffer" without further limitation or characterization ***is not*** also saline. Therefore, "buffered saline" is of a different scope and meaning as compared to "buffer" alone.

Moreover, even if one were to improperly ignore the entirety of the instant disclosure, merely based on the plain language meaning of the term "buffered saline", such a solution necessarily must comprise a buffering and salinity component. Under such a plain language interpretation, the terms at issue do have "buffer" as a commonality, but importantly, they differ in one aspect: the presence (or absence) of the term saline. *See* MPEP §2111. One of ordinary skill in the art will recognize he term "buffer" as a compound "that serves to maintain the free hydrogen ion concentration of the solution within a certain pH range, when hydrogen ions are added or removed from the solution." *See* pg. 7, lines, 23-25. The term "saline" plainly means comprising salt or being salty. Therefore, saline solutions as understood by one of ordinary skill in the art, in contrast to buffers, cannot maintain "the free hydrogen ion concentration of a solution", especially when hydrogen ions are added or removed from the solution. This is precisely why a buffering component is needed in order to accomplish this task. Furthermore, as disclosed in the instant disclosure, buffering components (i.e., buffers) are in fact added to a saline solution to provide a buffered saline solution. Similarly, a buffering compound or buffering solution alone does not comprise the salt or salinity component. Thus, the buffered saline solutions of the present invention, while providing a buffering function, are distinguished from a mere "buffer", because such solutions comprise the additional salinity or salt component.

Federal Circuit precedent supports the plain language interpretation of the term "buffered saline" and the need to interpret terms in their context. The Federal Circuit has consistently ruled that words of a claim should be "generally given their ordinary and customary meaning" when construing the terms of a claim. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005); quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). In *Phillips*, the Federal Circuit gave guidance as to the importance of context when determining the ordinary and

customary meaning of a claim term. *Phillips,* 415 F.3d at 1313-1314. The Court, in construing the claim term "steel baffles" noted that the ***context*** of this term within the claim was highly instructive to one of ordinary skill in the art when interpreting claim language:

> To take a simple example, the claim in this case refers to "steel baffles," which strongly implies that the term "baffles" does not inherently mean objects made of steel.

*Id.* at 1314. Thus, the Court emphasized the importance of context during claim interpretation by concluding that two words, when placed side-by-side, cannot be of the same meaning or same scope. The Court has in numerous instances emphasized the use of a term within a claim as a firm basis for interpreting claim language. *See, e.g., Mars, Inc. v. H.J. Heinz Co.,* 377 F.3d 1369 (Fed. Cir.2004); *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1356 (Fed. Cir. 1999).

As in *Phillips*, where the Federal Circuit noted that the term "steel baffles" cannot mean that baffles are inherently made of steel, the same conclusion can be drawn where the term "buffered saline" strongly implies that "saline" compositions are not inherently "buffered," or the converse that all "buffered" solutions do not inherently contain "saline." In other words, the term "buffered" is, and should be treated separately from the term "saline." Therefore, one of ordinary skill in the art, with guidance provided in the instant disclosure, would recognize that "buffered saline" and "buffer" do not have the same scope or meaning. Indeed, to interpret "buffered saline" to mean any "buffer" improperly ignores the limitation "saline" and as such, the Office's interpretation is incorrect.

Regarding the property of physiologically or pharmaceutically acceptable, the Office implies that "buffered saline" is not described as "pharmaceutically acceptable". Final Action, p. 2, ¶ 1. The Office cites a specific portion of the disclosure for lacking any description regarding "pharmaceutically acceptable", where in fact said portion of the disclosure is unambiguous in characterizing the term "buffered saline" as a *pharmaceutical excipient*. (Final Action, p. 2, citing Specification at p. 7, line 20). In this context, one of skill will recognize that the terms "pharmaceutically acceptable", "physiologically acceptable", "pharmaceutical excipient" or "pharmaceutical formulation" are essentially equivalents. Put another way, where the term "pharmaceutical" is utilized, one of ordinary skill in the art will recognize that such a formulation is intended to be administered to a subject, and not simply to sit on a shelf. Therefore, if the term

"buffered saline" were to be given its broadest interpretation, in considering the full instant disclosure and knowledge in the art, then such a limitation certainly includes "pharmaceutically acceptable".[1] Furthermore, if a formulation is pharmaceutically acceptable, then it logically follows that it is also physiologically acceptable for human use.

In addition, it should be noted that it is entirely improper for the term "buffered saline" to be construed in isolation and to the exclusion of the full disclosure. There is ample description for "buffered saline", where the claims recite and the specification further expounds upon the meaning of, "buffered saline", within the context of the present invention's pharmaceutcial botulinum formulation. For example, both claims 1 and 16 recite "buffered saline" and the specification (page 7) explains that a pharmaceutical excipient includes physiological buffer or buffered saline. Furthermore, such pharmaceutical excipients form part of the claimed formulation in said claims and are art recognized as physiologically acceptable. Indeed, the artisan should at once recognize that the term "pharmaceutical" encompasses administration to a subject.

In other words, one of ordinary skill after assessing the entire disclosure, and in view of what is known in the art, will recognized that the "buffered saline" of the present invention is characterized to be pharmaceutically or physiologically acceptable. Further, the disclosure is replete with teachings directed to the present invention's formulation as being "pharmaceutically acceptable". For example, both the claims and the specification are directed to and encompass a *pharmaceutical formulation for therapeutic use.* (e.g., claims 1 and 16; Specification, pp. 15-19, 25-29). As to "pharmaceutically acceptable" buffers and "buffered saline", the specification describes that the pharmaceutical formulation is comprised in a "buffered saline" or "physiological buffer". (e.g., Specification, p. 7, l. 20). Moreover, additional descriptions of physiological buffers are present in the specification (e.g., p. 7, ll. 28-30).

In view of the foregoing, Applicants respectfully submit that the claim interpretation set forth by the Office is incorrect and should be reconsidered.

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[1] The Office cites MPEP 2111 in stating "buffered saline" is to be given its broadest interpretation, but in doing so ignores an explicit limitation, i.e., saline, while concomitantly and inconsistently providing a narrow interpretation regarding pharmaceutical acceptability.

## IV. Claim Rejections Under 35 U.S.C. 112, Second Paragraph:

The Office rejects claims 1-28 under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. This rejection is respectfully traversed, because the claims are clear and definite. The rejection is rendered moot in regard to claims that are now canceled.

Claims 1 and 16 are rejected because it is alleged that it is unclear how "capable of being stable as a liquid" is different from "stabilized liquid". Insofar this rejection is directed to "stabilized" it is rendered moot by the instant amendment. The limitation "stable ready-to-use liquid" is clear and unambiguous as compared to "capable of being stable". One of skill will recognize that merely because a liquid is stable (e.g., containing a stabilizing agent) does not mean that such a liquid formulation is *capable of being stable* for prolonged time at a given temperature, which is an essential aspect of the invention as expounded upon throughout the disclosure.

Furthermore, claims 1 and 16 are rejected for lacking an article before the limitation "purified botulinum toxin". The claims are amended to include the article "a" before said limitation.

Claims 7 and 20 are rejected because it is alleged that it is unclear how "said buffered saline" is selected from a "buffer" Markush set. Claim 20 is canceled and claim 7 has been amended to clarify that a buffering compound in said buffered saline is selected from a group consisting of phosphate, phosphate-citrate and succinate buffer. In view of the amendments, it is clear that buffered saline is a solution comprising a buffering component and a salt or salinity component.

Claims 4 and 18 are rejected because it is alleged that "said buffered pH" lacks sufficient antecedent support. It is respectfully pointed out that the base claim recites a range for a given pH thus a buffered pH can indeed be a single measured pH, as long as it falls within the range defined by the base claim. Thus, where dependent claims recite a given pH that falls within the specified range, there is sufficient antecedent support. Therefore claims 4 and 18, pH 5.6 falls between pH 5 and pH 6 thus there is no ambiguity.

Claims 9, 11-13, 22 and 24-26 are rejected because they are allegedly not further limiting. One of skill will recognize that concentration provided in said claims further limits the therapeutic

concentration thus is further limiting. However, solely to advance prosecution, the claims have been amended to recite "said therapeutic concentration" and by no are intended to signal acquiescence to the instant rejection.

## V. Rejections Under 35 U.S.C. § 102

### A. The Sacks Reference Does Not Anticipate the Instant Claims Because It Does Not Disclose A "Buffered Saline", a "Pharmaceutical Botulinum Toxin Formulation", A "Stable Ready-to-Use" formulation or stability at between 0 and 10°C or for at least 6 months at a temperature between 10 and 30°C.

The Examiner rejected claims 1-3, 5-8, 16, 17 and 19-21 under 35 U.S.C. 102(b) as allegedly anticipated by Sacks *et al.* (Applied Microbiology 28:374-382, 1974). This rejection is rendered moot as to claims 2-3 and 6 as these claims are cancelled. Applicants respectfully traverse this rejection as to the currently pending claims that stand rejected.

The Office makes the following observations, each of which is addressed herein below:

> The limitation 'for therapeutic use in humans' in the base claims represents the intended use of the claimed product. The limitation in the dependent claims 7 and 20: 'said buffered saline is selected from the group consisting of .....buffer .....' indicates that the term 'buffered saline' recited in the base claims is equivalent to each of the 'buffer' recited in the dependent claims. Therefore, the limitation 'buffered saline' is interpreted as being same as 'buffer' in this rejection. The phrase 'the formulation is .... stable .... degrees centigrade ...' in the instant claims is viewed as a functional limitation that does not define the formulation structurally. It is noted that instant claims do not place a dose/concentration limit to the recited 'therapeutic concentration suitable for use in humans'. It is noted that the term 'stable' is defined at lines 15-17 of page 6 of the specification as referring to retention of biological activity or potency by a biologically active substance, specifically botulinum toxin, over a defined or indefinite period of time. While the term 'stabilized .... formulation' does not appear to exist in the instant specification, the term 'stable' is not associated with, or limited to, or equated to a specific degree of retention of biological activity of a botulinum toxin, or a specific percentage of potency. (Final Action, p. 10)

Regarding the Office's allegation that the limitation "therapeutic use in humans" represents an 'intended use', while the formulation is intended to be utilized in therapy, the limitation at issue is more than mere intended use. In fact, as is disclosed throughout the specification (e.g., p. 3, ll. 8-20, 24-30; ; p. 6, ll. 8-13, 15-18; p. 13, ll. 5-14), the formulation is ready-to-use and as such must comprise properties that correlate to therapeutic use, such as toxin concentrations that would be therapeutic as opposed to lethal. Put another way, in claims 1 and 16, the preamble does more than merely state a purpose or intended use for the invention, but rather, defines a property for the

pharmaceutical formulation. *See Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333-34, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003) (describing where the preamble is not always merely a statement of effect). Indeed, it is entirely appropriate to rely on the preamble to define, in part, the claimed invention. *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808-809, 62 USPQ2d 1781, 1785 (Fed. Cir. 2002). In the present claims, the limitation "for therapeutic use in humans" partly defines the stable ready-to-use liquid pharmaceutical formulation by characterizing the formulation as ready to be directly administered to a subject. Therefore, the limitation "therapeutic use in humans" must be considered when examining any prior art.

Next the Office asserts that because claims 2 and 20 recite that "buffered saline" is selected from a "buffer" then the limitation "buffer" is interpreted to be the same as "buffered saline". Claim 20 is canceled. As discussed above in the section under Claim Interpretations, the Office's interpretation of "buffered saline" is contrary to all that is disclosed in the instant application and contrary to the plain meaning of said limitations. Furthermore, the Office submits contradictory and inconsistent positions, where it both asserts that it cannot interpret claim 2 (i.e., under § 112, second paragraph, the claims are vague and indefinite), but interprets as the same "buffered saline" and "buffer", because of the same exact language in claim 2. Notwithstanding such contradictory positions set forth in the Final Action, claim 2 is amended to better characterize the present invention, i.e., indicating that the buffering component of the buffered saline is selected from the recited group, which squarely fits with the plain language interpretation of "buffered saline".

The Office also asserts that "[t]he phrase 'the formulation is .... stable .... degrees centigrade ...' in the instant claims is viewed as a functional limitation that does not define the formulation structurally." *Id.* It is respectfully submitted that to ignore said limitations is to ignore essential features that define an important aspect of the present invention. As the MPEP states, "A functional limitation must be evaluated and considered...for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used." MPEP § 2173.05(g). In the instant case, the limitations at issue define properties that distinguish the present invention over the prior art. Therefore, contrary to what the Office asserts, the limitations at issue do further define a structural (i.e., compositional) property for the pharmaceutically acceptable buffered saline.

In addition, the Office notes that a dose/concentration limit is not present. It is not clear what is being implied here. It should be noted, the relevant prior art provides that given the toxicity and lethality of undiluted or stock solutions of toxin, low concentrations or highly diluted concentrations are required to be therapeutic and not lethal/toxic. Indeed, the Office acknowledges this fact where it essentially states that low concentrations equal therapeutic concentrations. See, Final Action, p. 7, line 18. It is against a backdrop composed of the foregoing discussion that the Sacks reference must be examined.

The Office alleges that Sacks discloses a buffer with "sufficient overlap to reasonably conclude that the two formulations are one and the same in comparing the buffer in Sacks versus the "buffered saline" of the present invention. Final Action, p. 11, next to last sentence. It is respectfully submitted that the standard for anticipation is whether every limitation is disclosed in the prior art reference, not whether there is some degree of overlap. In the instant case, Sacks discloses a botulinum toxin formulation that is present in phosphate buffer, not phosphate buffered saline as in the present invention. Instead, the Sacks article discloses botulinum toxin in the absence of a saline environment. *See, e.g.*, pg. 4, 3rd full paragraph. Thus on this fact alone, Sacks cannot anticipate the instant claims. As explained above under the section Claim Interpretation, and as what one of ordinary skill in the art would understand, phosphate buffer does not equate to a "buffered saline." Because the Sacks article does not disclose a buffered saline, it cannot anticipate the instant claims.

Applicants also disagree with the Office's assessment that the pH 6.0 botulinum toxin E preparation disclosed in Sacks is "stable." Sacks notes that the liquid formulation stored in pH 6.0 phosphate buffer for 1 year at 4.0 °C "lost more than 60% of its original lethality." One of ordinary skill in the art, with guidance from the specification, will recognize that a loss of 60% of the original lethality is not a stable formulation. In fact, this amount is equivalent to the large losses found in prior art formulations, where losses of 44% and 70% of potency were reported in reconstituted botulinum toxin A formulations. *See* pg. 2-3 of the application. Therefore, one of ordinary skill in the art would not consider this formulation to be "stable." In contrast, the instant amended claims require that the stabilized liquid botulinum toxin formulation be "capable of being stable when

stored" at the recited temperature and time limitations. The Sacks reference does not disclose a stabilized liquid botulinum toxin formulation that meets these requirements.

In addition, Sacks discloses highly concentrated formulations of botulinum toxin that would not be considered by one of ordinary skill in the art to be a " **ready-to-use** liquid ***pharmaceutical*** botulinum toxin formulation" for therapeutic use or suitable for use in humans. The formulations disclosed in the Sacks reference cannot be considered to be a ***pharmaceutical*** formulation, nor are such formulations suitable ***for therapeutic use in humans***, precisely because of Sacks' formulation would be lethal, and would actually be considered to be a stock solution from which pharmaceutical formulations are made, and not a "ready-to-use" formulation. *See, e.g.,* instant specification, pg. 13, lns. 20-25; Schantz *et al.*, EP 0 593 176 at pg. 3, lines 22-24 (already of record). In other words, the formulation is also not **ready-to-use** thus failing to meet yet another limitation of the instant claimed invention.

In addition, the Office alleges that at least one of the non-peak fractions of the "aged" purified toxin is expected to contain purified botulinum toxin in a therapeutic concentration range that is suitable for use in humans. Thus, the Office submits speculation that the nonpeak fraction maintains enough activity to be therapeutic, without any supporting evidence or scientific reasoning. Furthermore, it is unclear how the Office has determined that said fraction has activity in a "therapeutic concentration range", where Sacks does not disclose any such information or data for said nonpeak fraction.

As was mentioned above, the specification gives sufficient guidance and teaching to one of ordinary skill in the art in regards to the contents of a "liquid pharmaceutical botulinum toxin formulation" and "a therapeutic concentration of purified botulinum toxin" to exclude concentrated toxin formulations eluted from a purification column chromatography column, as is the case for the Sacks reference. Applicants respectfully submit that the Sacks formulation is not a "liquid pharmaceutical botulinum toxin formulation," and therefore does not anticipate the instant claims.

Lastly, as explained above, the alleged functional limitations for stability at the delimited temperatures and/or time periods define the structural or compositional properties for the instant invention which correspond to the stable ready-to-use pharmaceutical formulation comprising

buffered saline. Therefore, said limitations are not inherent properties that are found in Sacks' buffer comprising any concentration of botulinum toxin, but rather, said limitations correspond to the present invention's buffered saline formulation.

Thus, in view of the foregoing, Applicants respectfully request that the Office withdraw this rejection.

**D. The Schantz Reference Does Not Anticipate the Instant Claims Because It Does Not Disclose a "Buffered Saline", A "Stable Ready-to-Use" formulation or stability at between 0 and 10°C or for at least 6 months at a temperature between 10 and 30°C.**

The Office has rejected claims 1-8, 12-21 and 25-28 under 35 U.S.C. 102(b) as allegedly anticipated by Schantz *et al.* (EP 0 593 176 A2). Applicants respectfully traverse this rejection.

The claim interpretations set forth above are incorporated herein in their entirety as applicable to the instant rejection, especially regarding the distinctness of "buffered saline" versus "buffer". Furthermore, the rejection is rendered moot insofar as it was applied to claims that are now cancelled.

The Office alleges that Schantz *et al.* discloses a pharmaceutical composition comprising crystalline botulinum toxin type A in buffers of about pH 5, pH 5.5. and pH 6.2. Furthermore, the Office alleges that Schantz discloses a pharmaceutical botulinum composition having pH 5.0 and pH 5.5. However, none of said formulations comprise a "buffered saline" as recited by the instant claims. On the contrary, the Schantz reference specifically requires the disclosed liquid botulinum toxin formulations compositions to be "sodium chloride free." *See, e.g.*, Abstract; pg. 2, lines 44-46; claim 1. The Schantz reference specifically teaches that "[t]he most critical factor was the absence of sodium chloride in the solution." *See* pg. 4, lines 1-2. Moreover, in comparing all experimental conditions used in the Schantz reference, it is clear that not a single experiment is conducted using the combination of a solution with a pH between pH 5 and pH 6 *and* saline. *See* Table 1 at pg. 5. Therefore, because the Schantz reference fails to disclose the use of a ***buffered saline*** at the recited pH ranges claimed, it does not anticipate the instant claims.

Furthermore, regarding the alleged functional limitations delimiting stability at the recited temperatures and/or time periods (e.g., claims 1 and 16), it is respectfully asserted that said limitations further define the instant inventive formulation thus are not properties inherent in any and all prior art buffers, as the Office implies.

In addition, the reference teaches that the toxin is lyophilized and reconstituted in distilled water prior to use. (p. 3, l. 46). Furthermore, the reconstituted formulation must first be assayed for toxin activity (p. 5, Table 1), thus does not meet the **ready-to-use** limitation.

In view of the foregoing, Applicants respectfully request that this rejection be withdrawn.

## VI. Rejections Under 35 U.S.C. § 103

### A. The Combination of Schwarz in view of Schantz *et al.* Fails to Meet the Prima Facie Requirements for Obviousness

The Office has rejected claims 1-9, 11, 16-22 and 24 under 35 U.S.C. §103(a) as being allegedly unpatentable over Schwarz, further in view of Schantz *et al.* Applicants respectfully traverse this rejection.

The claim interpretations set forth above are incorporated herein in their entirety. The rejection is rendered moot insofar as it was applied to claims that are now canceled.

In order to establish a prima facie case of obviousness, the Examiner must satisfy three basic criteria: 1) there must be some suggestion or motivation to modify or combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references combined must teach or suggest all of the claim limitations.

Whether combined or individually Schwarz and Schantz do not teach every claimed limitation. In particular, the references combined do not teach the limitation of a "buffered saline" solution as recited in independent claims 1 and 16. Moreover, the references when combined actually teach against away from "buffered saline". In particular, Schantz *et al.*, as mentioned above, teaches against the use of a buffered saline by specifically requiring the compositions to be "sodium chloride free." *See, e.g.*, Abstract; pg. 2, lines 44-46; claim 1. The Schantz reference

specifically teaches that "[t]he most critical factor was the absence of sodium chloride in the solution." *See* pg. 4, lines 1-2.

In addition, the references individually or combined do not teach the limitations wherein the claimed formulation is stable at a temperature between 0 and 10°C or for at least about 6 months at a temperature between about 10 and 30°C. As discussed above, said limitations define the formulation and are not inherent effects of prior art formulations, because such prior art formulations are not "buffered saline".

Furthermore, the references individually or combined do not teach the limitation for "ready-to-use" liquid formulation. Schwarz teaches that pH adjustment is conducted via Sephadex G25 columns and not through dilution of the crude and chromatography purified toxin preparations. (p. 3, first full paragraph). Therefore, the reference does not teach a formulation that is **ready-to-use** for therapeutic use in humans. Indeed, Schwarz teaches a formulation that is and would be lethal if administered to a would-be patient. The Schwarz solution is a stock solution that fails to meet the limitations of **stable ready-to-use** formulation for theapeutic use, and comprising **buffered saline**.

For the reasons above, Applicants respectfully submit that the Office has failed to establish a prima facie case of obviousness. Applicants hereby request that the Office withdraw this rejection.

## VII. Rejections under 35 U.S.C. § 112

### A. Written Description/New Matter

Independent claims 1 and 16, and dependent claims 6, 7, 19 and 20 are rejected as containing subject matter that was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed had possession of the claimed invention. With respect to independent claims 1 and 16, it is alleged that the limitations *stabilized, capable of being* [stable], and *to the formulation* are not supported by the instant disclosure. Furthermore, regarding dependent claims 6, 7, 19, and 20, it is allgeged that the limitation *buffered saline* is not supported by the instant disclosure. This rejection is respectfully traversed as to each of the preceding limitations, which the Office alleges to be new matter.

However, insofar as the rejection is directed to the limitation "stabilized", the rejection is rendered moot by instant amendments.

It is well settled that the proscription against the introduction of new matter serves to prevent an applicant from adding information that goes beyond the subject matter of the originally filed application. See, *e.g., In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323, 326 (CCPA 1981) and MPEP § 2163.06. Furthermore, it is axiomatic that any written description inquiry is dependent on the particular facts of the case. *Vas-Cath, Inc.* v. *Mahurkar,* 19USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim,* 191 USPQ 90 (CCPA 1976). The facts that must be taken into account include the disclosure as a whole and the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. *See, e.g., In re Lukach,* 169 USPQ 795,796 (CCPA 1971); *In reLange,* 209 USPQ 288 (CCPA 1981). Moreover, it is well settled patent law that "[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require literal support for the claimed invention...the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case of lack of adequate descriptive support...". *Ex parte Parksi,* USPQ2d 1234, 1236 (Bd. Pat. App. Int. 1994). Indeed, the subject matter of the claim can be supported in the specification through express, implicit or inherent disclosure. MPEP § 2163.

All that is necessary, as explained in *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, is for an applicant to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. Therefore, "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention a the time of filing, even if every nuance of the claims is not explicitly described in the specification..", then the written description requirement is met. *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

In the instant case, the subject matter added does not go beyond the subject matter present either explicitly or implicitly in the instant application as filed. The rejection set forth under 35 U.S.C. 112, written description, fails to consider the instant disclosure in its entirety and further

improperly requires literal recitation of every claimed limitation. Furthermore, the Final Action states, "[t]here appears to be no support in the instant specification, as originally filed that provides descriptive support for *the* new limitation." (emphasis added) (Final Action, p. 4, middle). As a preliminary matter, it must be noted that it is unclear to which limitation the Examiner is referring as the rejected claims 1 and 16 comprise *multiple limitations* added by amendment. Therefore, the preceding statement does not identify the claim limitation at issue as the initial burden on the Examiner requires. MPEP § 2163.04.

The Office's additional assertions do identify "stabilized" and "capable of being" as alleged limitations that lack descriptive support. More specifically, the Examiner asserts that "[t]he term 'stabilized'...does not appear in the specification, as originally filed." (Final Action, p. 4, middle). The Office does not provide any additional factual, scientific or legal evidence to show by the preponderance of the evidence that the instant disclosure fails to convey to one of skill in the art that Applicants are not in possession of the term "stabilized" in the context of the pharmaceutical formulation, but are in possession of "stable" in the same contextual.

The Office solely relies on a grammatical nuance for the term "stable" versus "stabilized" as the basis for the new matter rejection. The instant disclosure provides sufficient support for all the amendments alleged to be new matter. Furthermore, the instant disclosure is replete with description for the limitation "stabilized" wherever the term "stable" is present, because one of skill would not distinguish the two in the context of the pharmaceutical composition. (e.g., claims 1 and 16; the Title of the invention; Abstract; p. 3, ll. 13-29; p. 5, ll. 15-30; p. 6, ll. 8-15; p. 13, ll. 4-18). One of ordinary skill will recognize that the plain meaning of the term "stable" includes grammatical nuances for the same, such as "stabilized". At the simplest level, the term "stable" is a noun, where "stabilize" is the corresponding verb, and "stabilized" is merely an inflected form of the same. Indeed, the artisan would recognize that "to make stable", "stable", or "stabilized" are equivalents for the purposes of the pharmaceutical formulation of the present invention. The suggestion that "stabilized" does not equate to "stable" absolutely contravenes the plain meaning of "stabilized". *See*, Webster's OnLine Dictionary, Available at <http://www.m-w.com/dictionary/stabilized> (last accessed, April 21, 2006) (defining *stabilized* to mean to make *stable* or to become *stable*).

Further, the Examiner appears to be requiring a literal or explicit recitation of the term "stabilized" as the basis of the rejection and the written description rejection. First, as noted above, the law only requires that the full disclosure in light of what is known in the art must convey to the artisan that applicants are in possession of what is being claimed. Therefore, there is no requirement for exact literal support for the term "stabilized". Further, given the plain meaning of the terms "stable" and "stabilized", and after assessing the entirety of the instant disclosure in view of what is known in the art, the artisan would not find the two terms distinct in the context of the pharmaceutical formulation. Other than pointing out that the term "stabilized" is not recited in the specification as filed, the Office does not submit any factual or reasoned basis why one of skill would not recognize "stabilized" as equivalent to "stable". Most interestingly, the Office while alleging that "stable" and "stabilized" are distinct in making the new matter rejection, concomitantly equates "stable" to "stabilized". See, Final Action, p. 11, l. 7 (reciting "stable (i.e., stabilized)"). How can the Office submit this rejection while acknowledging that "stable" and "stabilized" mean the same thing? Because the terms "stable" and "stabilized" are mutually inclusive, it is respectfully asserted that the rejection is improper and should be withdrawn.

With respect to the limitation "capable of being" as further characterizing the formulation, the Examiner does not set forth any explanation as to why this limitation lacks support. First, as explained above, the terms "stable" or "stabilized" are not so distinct that one of skill in the art would not recognize that a formulation that is "stable" also includes "stabilized" within the plain meaning of the terms. Furthermore, it logically follows that if something is stabile or stabilized then it is clearly "capable of being" stable. In any event, the Examiner's attention is directed to page 7 where it is stated:

> The term "liquid pharmaceutical formulation" refers to a pharmaceutically active preparation of drug or biological which is *capable of being stored* in a liquid pharmaceutical excipient, such as buffered saline or a physiological buffer, *for an extended period of time*. The formulation may be a concentrated formulation which is diluted in a similar or different liquid prior to use. (emphasis added)

One of ordinary skill in the art familiar with botulinum toxin and its instability at pharmaceutical formulations (i.e., low concentrations) would recognize that if such a formulation is stated to be *capable of being stored for an extended period of time*, then such a formulation is, at

minimum implied to be if not explicitly so, "stable" or "capable of being stable". The artisan in this case is someone who is familiar with botulinum formulations and their instability at pharmaceutical or therapeutic concentrations, who is a clinician with a Ph.D. or M.D. degree. In view of the foregoing, it is respectfully asserted that rejection of the limitation "capable of being" as lacking sufficient description is improper and should be withdrawn.

Regarding the limitation "to the formulation" further characterizing the "buffered saline" and the formulation, the Office appears to be taking the position that "buffered saline" cannot mean "buffer". In particular, the Office asserts that the various passages in the specification describing a buffer solution having a buffering agent and a salt (i.e., buffer) provide a buffered pH range to the formulation. (Final Action, p. 4, last paragraph). Once again, it appears a literal recitation is sought where none is needed. Essentially, the Examiner is arguing that the succinate and NaCl, a buffering and salinity agent respectively, somehow equate to a buffer, but not a "buffered saline". Upon reading the entirety of the instant disclosure, one of ordinary skill in the art will recognize that in the context of the pharmaceutical formulation of the present invention, the limitation "buffered saline" is not exclusive from providing buffering capacity in the disclosed pH ranges and salinity. In other words, if the formulation is to be stored for an extended period of time and remain a "pharmaceutical" and where such a formulation comprises a buffered saline solution, then one of skill will recognize that the "buffered saline" is a buffer for the purposes disclosed in the instant disclosure.

In contrast to the meaning of the terms "buffer" and "buffered saline" as disclosed in the instant specification and explained further herein above, essentially the Office asserts that "buffered saline" is not a buffer, or that the succinate/NaCl buffer (i.e., buffered saline) cannot be considered "buffered saline", notwithstanding that the buffer disclosed on pages 20 and 21 of the specification contains a buffering agent (e.g., succinate) and a salt (NaCl). In other words, if one were to accept the Office's position, then a "buffered saline" such as succinate/NaCl, which is capable of providing buffering capacity to a liquid formulation, is actually not a buffer. While the specification is replete with implicit or inherent disclosures providing support for the above mentioned limitations, there is also ample explicit support for the same.

For example, on page 14, the specification recites the following paragraph (beginning on line 3):

> The diluent referred to above can be any pharmaceutically acceptable liquid which will not adversely affect the stability of the complex, and which supports a stable pH range between about pH 5 and pH 6. Examples of particularly suitable buffers include succinate and phosphate buffers; however, those of skill in the art will recognize that formulations of the invention will not be limited to a particular buffer, so long as the buffer provides an acceptable degree of pH stability, or "buffer capacity" in the range indicated. Generally, a buffer has an adequate buffer capacity within about 1 pH unit of its pK. (Lachman, *et al.*, 1986). In the context of the present invention, this includes buffers having pK's in the range of about 4.5-6.5. Buffer suitability can be estimated based on published pK tabulations or can be determined empirically by methods well known in the art. In addition to the succinate and phosphate buffers mentioned above, other pharmaceutically useful buffers include acetate, citrate, aconitate, malate, and carbonate (Lachman). The pH of the solution can be adjusted to the desired endpoint within the range using any pharmaceutically acceptable acid, for example hydrochloric acid or sulfuric acid, or base, for example sodium hydroxide.

Reading the entirety of the instant disclosure, along with the cited passage above, it becomes clear that a "buffered saline" is certainly a buffer in so much as it provides buffering capacity. In this vein, it should also be clear that a buffer alone does not necessarily or by definition also comprise a salt (i.e., a buffered saline is a buffer but a buffer does not necessarily comprise a salt, such as NaCl).

In addition, the above noted passage is under the section heading "Stable Botulinum Toxin Formulation" further signaling to the artisan that the *pharmaceutically acceptable liquids* (Specification, p. 14, line 3) comprising the formulation include liquids with buffering capacity, such as those comprising succinate or phosphate. Furthermore, on page 7, the specification identifies such pharmaceutical liquids as comprising a "buffered saline". (p. 7, ll. 18-20). Therefore, the instant disclosure does provide support for the instant amendments by at least a preponderance of evidence, through either the implied or explicit references to "buffers", "buffered saline" and

"pharmaceutically acceptable liquids" as disclosed in the specification and explained above. In sum, it is unclear how one of ordinary skill in the art can assess the entirety of the instant disclosure, including the passage above, and yet conclude that "buffered saline" does not have buffering capacity between pH 5 to pH 6, or that a buffer comprising succinate added to a saline solution is not a "buffered saline". Thus, in view of the foregoing, it is respectfully asserted that the new matter rejection of the limitation "to the formulation" is improper and should be withdrawn.

The Office has also rejected claims 6, 7, 19 and 20, because it is alleged that the limitation "buffered saline" lacks any support in the specification. (Final Action, p. 5). It is respectfully submitted that the specification provides literal support and/or implicit support throughout for the limitation "buffered saline" in the context of the pharmaceutical formulation of the present invention. (e.g., p. 3, ll. 24-28; p. 4, ll. 15-16; p. 7, ll. 18-21; p. 14; p. 21 and Table 1). Furthermore, there is both explicit and/or implicit support for buffering capacity to be in the claimed pH range of about 5 and 6. (e.g, p. 3, ll. 25-30; p. 7, ll. 25-31; p. 13, ll. 20-25; p. 14, ll. 4-18; Example 1; Tables 2 and 3; p. 22, ll. 15-22).

Therefore, one of ordinary skill in the art, in assessing the instant disclosure in its entirety and assessing the information that is known in the prior art, would come to the determination that the instant inventors are in the possession of "buffered saline". At minimum, the term is explicitly recited in the specification (p. 7, l. 20) thus Applicants have every right to claim the invention accordingly. Further, as explained above, a "buffered saline" comprises buffering capacity thus meets the functional requirement for a buffer.

In view of the foregoing, it is respectfully submitted that the new matter rejection over the limitation "buffered saline" is improper and should be withdrawn.

**B. <u>Scope of Enablement</u>**

The Office has rejected claims 1-14 and 16-27 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not teach how to make and use the full scope of the invention. This rejection is respectfully traversed.

The interpretations of the claims discussed above are incorporated herein in their entirety. The rejection is rendered moot insofar as it was applied to claims that are now canceled. Furthermore, the Office asserts one ground of unpredictability on the "buffered saline" of the invention with respect to whether such a formulation comprises a protein excipient, such as gelatin or human serum albumin. See, Final Action, pp. 6-8. This assertion is rendered moot as all the claims are now delimited to comprising human serum albumin.

The Office also states, "there is no predictability that 'a therapeutic concentration' of other types of botulinum toxin, such as, types A, C1, C2, D, E, F and G, when formulated as a liquid pharmaceutical formulation as recited in the instant claims would be capable of remaining stable at the recited temperature range for the recited duration of time." Final Action, p. 9. The Office does not set forth any additional scientific basis on which the enablement rejection is couched.

The Office also asserts that the succinate buffered saline of Example 1 neither amounts to isotonic saline nor physiologic saline. See, Final Action, p. 7, bottom paragraph bridging to p. 8. There is no further explanation of how this statement is relevant to either "buffered saline" with/without protein excipient, or the different serotypes of botulinum toxin, which are expressed as the grounds for the scope of enablement rejection. Nor is there any further clarification if this assertion is somehow relevant on its own. Applicants can only assume that the Office deems this aspect important. Therefore, the Office alleges that the enablement requirement is not met for all serotypes claimed and that buffered saline is not isotonic or physiological.

***1. Different Serotypes of Botulinum Toxin***

With respect to the various serotypes, the Office alleges that a review of the post-filing art indicates that those of skill in the art have not shown the stability features demonstrated with commonly utilized toxin serotypes (e.g., botulinum B or A) as applicable or reproducible with other serotypes. Furthermore, the Office implies that working examples are needed for each serotype for the claims to be enabled. Final Action, p. 9, ll. 14-15. In addition, the Office alleges that there is a lack of specific disclosure and/or guidance and the lack of evidence. The Office also alleges an undue level of experimentation but does not elaborate as to what such experimentation entails, but

merely provides a conclusory statement that "[t]he ability to reproducibly practice the full scope of the claimed invention is well outside the realm of routine experimentation." Final Action, p. 9.

It is respectfully asserted that it would be routine to obtain/purify various serotypes of botulinum toxin and to use such isolated toxin to compose a liquid formulation utilizing the stable ready-to-use formulation comprising buffered saline of the present invention. The level of experimentation is remedial, in that the clinician (likely with a PhD or MD degree) would determine the activity of the primary isolate to determine the Units or $LD_{50}$, regardless of the type of botulinum (i.e., serotype). Once the base line activity is determined, the toxin will be diluted accordingly by one or more methods disclosed in the instant application, utilizing the buffered saline formulations of the invention.

As the prior art of record makes clear, each of the claimed serotypes are simple proteins which are only distinguished as to the type of *C. botulinum* bacteria from which they are isolated. See, *e.g.,* Schantz and Sugiyama, J. Agr. Food Chem. 1974; 22(1): 26-30, p. 26. The Office cites Grethlein et al. for the proposition that liquid formulations utilized for type B are not applicable or reproducible as to other types. However, Grethlein et al. does not explicitly or implicitly asses any such unpredictability or lack of reproducibility. In fact, the reference is limited to type B only. Therefore, the reference is not probative with respect to unpredictability amongst the various claimed serotypes.

In addition, that each toxin is structurally different is not in and of itself any more relevant than the assertion that one protein has a different amino acid sequence as compared to another. The Office asserts generally that because each serotype is structurally and pharmacologically different, then there is an insurmountable level of unpredictability. Final Action, p. 9, l. 6. However, the references cited do not actually support the assertion that there would be unpredictability in obtaining/isolating various serotypes and mixing them with *the instant formulation. Id.* (citing Moyer et al; Jankovic et al. and Dekker). In other words, the Office has not offered any scientific-based reasoning or any evidence supported by the relevant art that concludes or even suggests that various simple botulinum proteins that can be isolated through methods known in the art, when mixed/diluted into a liquid formulation of the instant invention, would not be stable for the recited

times/temperatures. In fact, none of the cited references teach or suggest the instantly claimed buffered saline pharmaceutical formulation. Thus, to allege unpredictability, without more is simply speculation. It follows, if there is no scientific or legal basis for establishing unpredictability at a level that requires undue experimentation, there is no requirement to provide examples for each and every serotype of botulinum toxin.

As such, it is respectfully asserted, that the Office has not met its burden for establishing *prima facie* lack of enablement and the rejection should be withdrawn.

***2. Isotonic or Physiological***

As noted above, regarding the buffered saline of the present invention and the allegation that it is not isotonic or physiological, the Office's assertion is vague and ambiguous, because the only two basis for the enablement rejection articulated are limited to buffered saline not comprising a protein excipient (e.g., gelatin) and the number of botulinum serotypes. However, in the interest of advancing prosecution and addressing every concern the Office may have, Applicants will address this concern. Specifically the Office asserts that a succinate buffer containing 5.8 mg/mL NaCl and 0.5 mg/mL human serum albumin neither amounts to isotonic saline nor physiologic saline.

First, it is noted that none of the claims are delimited to "buffered isotonic saline" nor "isotonic saline" thus it is not clear why the office would raise this point in the first place. However, it is respectfully pointed out, that the cited buffer is isotonic, notwithstanding the lack of such a limitation requirement. For example, the buffered saline comprises 2.7 mg/mL disodium succinate (i.e., succinate buffering component), which in addition to 5.8 mg/mL NaCl totals in salinity to above 0.84% which is effectively isotonic. However, if for example, such a formulation is not isotonic to human blood, such a result would not mean that the formulation is not pharmacologically or physiologically acceptable. Indeed, one of ordinary skill in the art will recognize that saline even down to 0.5% will not necessarily cause hypotonicity instantaneously, where cells are placed in such an environment. Therefore, in the course of administration of the pharmaceutical formulation of the present invention to a subject, even if the formulation were not isotonic, and even if some red blood cells or other cells lyse in the microenvironment where therapeutic administration is made, such would not preclude therapeutic effects, and such would certainly not amount to a lack of

physiological or pharmaceutical acceptance. However, as discussed in the preceding explanation, the formulation is isotonic, thus physiologically acceptable. Moreover, it follows that whether the formulation is isotonic is less relevant to whether the formulation is physiologically acceptable. In sum, the formulation of the invention are both pharmaceutically and physiologically acceptable, as well as isotonic.

## CONCLUSION

In summary, Applicants submit that the references cited by the Office do not anticipate or render obvious the instant claims. Particularly, the references, either alone or in combination, fail to disclose:

- A stabile ready-to-use liquid botulinum toxin formulation for therapeutic use in humans comprising:
- A pharmaceutically acceptable
- Buffered saline between pH 5 and pH 6
- Which is capable of being stable for at least a year between 0 and 10 degrees centigrade, +/- 10%, or for at least 6 months between 10 and 30 degrees centigrade, +/- 10%.

In addition, with respect to claims 14 and 16, the Office submits art under §§ 102 and 103, however the cited references individually or in combination do not teach all the recited limitations: "stable ready-to-use" formulation, comprising buffered saline with "100mM sodium chloride", "10mM succinate buffer at a buffered pH of 5.6", 0.5 mg/mL human serum albumin", and "botulinum type B present at a concentration of 5,000 +/- 1000 U/mL.

Furthermore, the instant disclosure fully enables the instant claims and provides adequate written description for the same, as discussed herein above.

In light of the remarks set forth herein, Applicants believe that they are entitled to a letters patent. Applicants respectfully solicit the Examiner to expedite the prosecution of this patent application to issuance. Please charge any fee due in connection with this submission to Deposit

Account No. 23-2415. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 31242.701.201).

Respectfully submitted,

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